Remarks

Claims 1-5 and 7-28 herein are pending and are original or were previously presented. No new matter is added by the present response.

Claims are not anticipated

As a preliminary matter, Applicants believe that a brief description of independent claim 1 would be helpful, prior to characterizing each cited reference and comparing the claim to the references.

Claim 1 is directed to a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient, the therapeutic treatment includes chemotherapy, radiation therapy, surgery, and combinations of these. The method involves the steps of administering to the patient a therapeutically effective amount of a carbohydrate which binds to a galectin and administering the therapeutic treatment to the patient.

The Office Action on pp. 3-4 rejects claims 1-3, 13, 14, and 22 under 35 U.S.C. §102(b) in light of Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999). Applicants respectfully traverse.

The MPEP states that, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Manual of Patent Examining Procedure* § 2131 (8th ed., Rev. 4, Oct. 2005), *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q. 2d 1051, 1053 (Fed. Cir. 1987). Thus, the standard for rejection under 35 U.S.C. § 102 is identity.

Applicants show below that the subject matter of the present claims is different from the subject matter of Green et al. Green et al. shows that anti-adhesive molecules act *in vitro* as chemosensitizers (Green et al., p. 157 right column, 1st paragraph). For example, Green et al. shows that synthetic glycoamine analogs (Fru-Gly, Fru-D-Leu, and Lac-L-Leu) inhibit interaction of cells *in vitro* from four carcinoma cell lines (Ibid. p. 159 right column and p. 160 left column and Figure 2A and 2B).

In contrast to Green et al., claim 1 is directed to a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient. One step of the method of claim 1 involves

administering the therapeutic treatment to the patient. Green et al. shows only *in vitro*, i.e. cells in culture, experiments performed using cell lines only (Ibid. p. 160).

This reference fails to show any methods for treating patients. Green et al., merely states that additional experiments are underway in the laboratory to examine if glycoamines have any *in vivo* affects (Ibid. p. 161). However, these experiments are merely an advertisement for future work and not a showing. Further, as they are laboratory experiments, they are an advertisement for future animal studies and not a method for a therapeutic treatment of cancer patients.

Green et al. is not the same as the method of claim 1. Nowhere does Green et al. show any results for any *in vivo* experiments, let alone show any administering of any therapeutic treatment to any patient, let alone in a therapeutic dosage for a patient.

Therefore, Green et al. is not the same as claim 1 and does not anticipate claim 1 under 35 U.S.C. §102(b). Claims 2-3, 13, 14, and 22 depend directly or indirectly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter, and therefore also are not anticipated by Green et al.

Therefore rejection of claims 1-3, 13, 14, and 22 under 35 U.S.C. §102(b) can be withdrawn, an action which is respectfully requested.

The Office Action on p. 4 rejects claims 1-4, 7, 13, 18, 20, 22-26, and 28 under 35 U.S.C. §102(e) in light of Klyosov et al. (U.S. patent application number 2003/0064957, published in 2003).

To anticipate under 35 U.S.C. §102(e) the invention must have been described in an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent.

Klyosov et al. (2003) was filed March 27, 2002 and is a continuation-in-part of U.S. patent application serial number 09/818,596 ("Klyosov parent application"). The Office Action cites Example 3, however "Klyosov the parent application" lacks Example 3. The sections cited by the Examiner were added as new matter and do not have any earlier priority. As such, the earlier priority date (March 27, 2001) does not apply to sections of the specification of Klyosov et al. (2003) cited by the Examiner.

The present application is a continuation of U.S. patent application serial number. 10/176,235, which claims priority to U.S. provisional patent application serial number 60/299,991, filed June 21, 2001.

Therefore Klyosov et al. (2003) is not proper prior art and rejection of claims 1-4, 7, 13, 18, 20, 22-26, and 28 under 35 U.S.C. 102(e) and can be withdrawn, an action which is respectfully requested.

Claims are non-obvious

As a preliminary matter, Claim 1 is directed to a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient, the therapeutic treatment includes chemotherapy, radiation therapy, surgery, and combinations of these. The method involves the steps of administering to the patient a therapeutically effective amount of a carbohydrate which binds to a galectin and administering the therapeutic treatment to the patient.

Claim 23 is directed to a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient, the therapeutic treatment includes chemotherapy, radiation therapy, surgery, and combinations of these. The method involves the steps of administering to the patient a therapeutically effective amount of a carbohydrate which is made of a polymeric backbone having side chains dependent therefrom, which binds to a galectin, and administering the therapeutic treatment to the patient,

Claim 27 is directed to a method for enhancing the efficacy of a surgical treatment for cancer in a patient. The method involves the steps of administering to the patient a therapeutically effective amount of a carbohydrate made of a polymeric backbone having side chains dependent therefrom, the side chains being terminated by a galactose or arabinose unit, and administering surgery to the patient.

Claim 28 is directed to a method for enhancing the efficacy of an oncolytic chemotherapeutic in a patient. The method involves the steps of administering to the patient, prior to or concomitant with the oncolytic chemotherapeutic, a therapeutically effective amount of a carbohydrate made of a polymeric backbone having side chains dependent therefrom, the side chains being terminated by a galactose or arabinose unit, and administering the oncolytic chemotherapeutic to the patient.

Klyosov et al. (U.S. patent application number 2003/0064957, published 2003)

The Office Action rejects claims 1-4, 13, 18-26, and 28 under 35 U.S.C. §103(a) in light of Klyosov et al. (2003). Applicants respectfully traverse.

Klyosov et al. (2003) was filed March 27, 2002 and is a continuation-in-part of U.S. patent application serial number 09/818,596 ("Klyosov the parent application"). Example 3 and all references cited in the Office Action are new matter added at the time of filing Klyosov et al. (2003). Therefore, these added sections of Klyosov et al. (2003) have a filing date of March 27, 2002.

The present application is a continuation of U.S. patent application serial number 10/176,235 and claims priority to U.S. provisional patent application serial number 60/299,991, filed June 21, 2001. Therefore, the present application is accorded a priority date of June 21, 2001.

As such, Klyosov et al. (2003) is not proper prior art under 35 U.S.C. 103(a). Therefore rejection of claims 1-4, 13, 18-26, and 28 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Klyosov et al. (U.S. patent number 6,645,946, issued 2003)

The Office Action rejects claims 1-4, 7, 13, and 18-28 under 35 U.S.C. §103(a) in light of Klyosov et al. (U.S. 6,645,946; "Klyosov parent"). Applicants respectfully traverse.

Klyosov et al. shows a method for reducing toxicity of a toxic agent administered to a subject (Klyosov, Abstract lines 1-5). Klyosov et al. shows only the polysaccharide galactomannan, and shows sources of galactomannan, ratios of mannose to galactose, and ratios of galactomannan to a toxic agent (Ibid. column 5, lines 4-64).

Klyosov et al. fails to show treating cancer in a patient, as admitted in the Office Action on p. 6. Example 1 in Klyosov et al. shows injecting galactomannan and 5-FU intravenously to Albino Swiss mice (Ibid. columns 7-12). This Example merely shows reduced toxicity of 5-FU when injected with galactomannan compared to injection of 5-FU alone (Ibid. column 11, Table 1).

Example 2 in Klyosov et al. shows galactomannan and Adriamycin injected into Albino Swiss mice (Ibid. columns 12-14). Example 2 show only reduced toxicity of Adriamycin when

injected with galactomannan compared to injection of Adriamycin alone (Ibid. column 14, Table 2).

Nowhere does Klyosov et al. teach or suggest a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient, as admitted in the Office Action on p. 7. In fact, Klyosov et al. just shows a method for reducing toxicity. The Albino Swiss mice do not even have cancer, as admitted in the Office Action on p. 6. Further, the dosages are not therapeutically effective in a cancer patient.

The Office Action alleges that the same patient population would be treated regardless of whether the intent was to reduce side effects or enhance efficacy and that recognition of another advantage that would flow naturally from following the suggestion of the prior art cannot be a basis for patentability when the differences would otherwise be obvious. Applicants respectfully traverse for numerous reasons.

First, there are no cancer patients in Klyosov et al., so there can be no same patient population. Second, efficacy refers to the minimum amount of a drug or treatment capable of obtaining a thereapeutic result. In contrast, toxicity is a dose at which positive toxic affects are seen. In fact, for a drug to proceed through FDA clinical trials it must meet a certain therapeutic index, which is the measurement of the ratio of the dose range at which the drug shows efficacy divided by the dose at which it shows toxicity. Each measurement is independently made. Reducing toxicity by any of various means does not necessarily increase efficacy because these terms refer to different characteristics of a molecule that are assayed differently. For a good agent, these dosages are far apart. Therefore, claim 1 which is directed to a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient is not taught or suggested by Klyosov's method for reducing toxicity of a toxic agent.

Most important, Klyosov et al. fails to teach or suggest that galactomannan binds to any galectins; rather, Klyosov et al. merely proposes many different speculative mechanisms of action for the interaction of galactomannan and a toxic drug. For example, Klyosov et al. suggests a direct physical interaction between the drug and galactomannan by increasing membrane fluidity and permeability (Ibid. column 6 lines 8-13). Further, Klyosov et al. suggests that galactomannan may act to inhibit aggregation of tumor cells; it may act by inhibiting their adhesion to normal cells; it may act by preventing metastasis (Ibid. column 6 lines 14-17).

Further, Klyosov et al. suggests that the toxicity of the chemotherapy drug may be reduced because the drug is inactive as long as it is bound to polymer (Ibid. column 6 lines 18-23). Any suggestion regarding a galectin is mere speculation within a discussion that is a laundry list of many different possibilities.

Since Klyosov et al. proposes many possible mechanisms of action, one of ordinary skill in the art of biochemistry and molecular biology, reading Klyosov et al. at the time the present application was filed, would not have been taught that galactomannan binds to galectins.

Further, nowhere does Klyosov et al. teach or suggest a method for enhancing the efficacy of a surgical treatment for cancer in a patient. In fact, Klyosov et al. never mentions surgery, as the Office Action admits on p. 7. Even further, Klyosov et al. nowhere mentions oncolysis or radiation, which is the subject matter of claims 1, 23, 27, and 28.

For any of these reasons, claims 1, 23, 27, and 28 are not obvious in light of Klyosov et al. Claims 2-4, 7, 13, and 18-22, depend directly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter. Claims 24-26 depend directly from claim 23 and incorporate the subject matter of claim 23 and contain additional subject matter. Therefore, claims 2-4, 7, 13, 18-22, and 24-26 also are not obvious in light of Klyosov et al.

Therefore rejection of claims 1-4, 7, 13, and 18-28 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999)

The Office Action rejects claims 1-3, 13, 14, and 18-22 under 35 U.S.C. §103(a) in light of Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999). Applicants respectfully traverse.

Green et al. shows assays of malignant cells *in vitro* and the *in vitro* use of small molecular sugar-amino acids (Fru-Gly, Fru-D-Leu, and Lac-L-Leu) as chemosensitizers (Green et al., p. 157 right column, first paragraph). In an i*n vitro* experiment, Green et al. shows that adding the cytotoxic agent 4-HC and bovine testicular hyaluronidase to EMT-6 mouse cells resulted in increased susceptibility of the cells to the 4-HC (Ibid. p. 158 bottom left column and right column). However, 4-HC and bovine testicular hyaluronidase had no effect on the formation of cellular aggregates for human cells (Ibid. p. 158 bottom right column).

Green et al. also shows that synthetic glycoamine analogs inhibit interaction of cells from carcinoma cell lines (Ibid. p. 159 right column and p. 160 left column and Figure 2A and 2B).

Nowhere does Green et al. teach or suggest a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient. Green et al. shows only *in vitro* experiments on cells from different cell lines (Ibid. p. 159 right column and p. 160 left column). Nowhere does Green et al. teach or suggest any *in vivo* experiments, let alone a therapeutically effective amount for administration to a cancer patient. In fact, nowhere does Green et al. teach or suggest any method of treating a cancer patient.

Nowhere does Green et al. teach or suggest administering to the patient a therapeutically effective amount of any agent, let alone a carbohydrate which binds to any galectin and administering the therapeutic treatment to the patient. Green et al. merely used glycoamines in *in vitro* experiments. Therefore, Green's *in vitro* use of glycoamines would not have taught or suggested to one of ordinary skill in the art of biochemistry or molecular biology that these glycoamines act by binding galectins.

Further, Green et al. fails to teach or suggest any chemotherapy treatment with administration of any carbohydrate that binds a galectin in combination with surgery or radiation treatment. Green's glycoamine is merely a chemosensitizer, and that only *in vitro* (Ibid. p. 160 right column).

For any of these reasons, claim 1 is not obvious in light of Green et al. Claims 2-3, 13, 14, and 18-22 depend directly or indirectly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter, and therefore these claims also are not obvious in light of Green et al.

Therefore rejection of claims 1-3, 13, 14, and 18-22 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Rubin et al. (U.S. patent number 5,639,737, issued 1997)

The Office Action rejects claims 1-3, 12, 13, and 18-22 under 35 U.S.C. §103(a) in light of Rubin et al. (U.S. patent number 5,639,737). Applicants respectfully traverse.

Rubin et al. shows methods and compositions for treating malignant tumors and inhibiting metastases (Rubin et al. column 1 lines 16-19). Rubin et al. uses lactose, or lactose

conjugated cytotoxic agents for preventing metastases (Ibid. column 6 lines 10-27) and shows procedures for conjugating lactose to a cytotoxic drug (Ibid. column 7 and 8). Rubin et al. also shows methods of manufacturing sugar conjugates (fructose, glucose, and galactose) and methods of increasing sugar conjugate activity (Ibid. columns 9-11).

Nowhere does Rubin et al. teach or suggest administering to the patient a therapeutically effective amount of a carbohydrate which binds to a galectin. One of ordinary skill in the art of biochemistry or molecular biology, reading Rubin et al. at the time the present application was filed, would not have been taught that the mechanism of action is binding to galectins. In fact, Rubin et al. is silent regarding galectin-binding, as the Office Action admits on p. 9. The word "galectin" simply is not mentioned in Rubin et al.

For at least this reason, claim 1 is not obvious in light of Rubin et al. Claims 2-3, 12, 13, and 18-22, and 18-22 depend directly or indirectly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter, and therefore also are not obvious in light of Rubin et al.

Therefore rejection of claims 1-3, 12, 13, and 18-22 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999) or Rubin et al. (U.S. patent number 5,639,737, issued 1997) in view of Platt et al. (PCT patent application number WO 97/34907, published 1997)

The Office Action rejects claims 1-5, 7-9, 12, 13, and 15-28 under 35 U.S.C. §103(a) in light of Green et al. or Rubin et al. in view of Platt et al. Applicants respectfully traverse.

Green et al. and Rubin et al. are characterized above. Platt et al. fails to cure any of the defects of Green et al. or Rubin et al. alone or in combination, as is shown below.

Platt et al. shows a modified pectin and the chemical characteristics of modified pectins. (Platt et al. p. 1 lines 7-9 and p. 2 line 4 to p. 3 line 8). Platt et al. also shows methods of making a modified pectin (Ibid. p. 5 line 22 to p.7 line 8).

Nowhere does Platt et al. teach or suggest a method for enhancing the efficacy of a therapeutic treatment for cancer in a patient, the therapeutic treatment including chemotherapy,

radiation therapy, surgery, and combinations of these. In fact, the words "chemotherapy", "radiation therapy", and "surgery" are simply never used in this reference.

Nowhere does Platt et al. teach or suggest administering to the patient a therapeutically effective amount of a carbohydrate which binds to a galectin and administering the therapeutic treatment to the patient. Platt et al. never uses the word "galectin". Platt et al. shows only methods of making a modified pectin. Never does this reference teach or suggest any method for treating cancer in a patient, by administering a carbohydrate which binds to a galectin, or administering a therapeutic treatment to a patient.

To establish a *prima facie* case of obviousness, a reasonable expectation of success must be found in the prior art, and not based on Applicants' disclosure. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 916 F.2d 680, 16 U.S.PDQ 1430 (Fed. Cir. 1990).

Applicants show below that none of the prior art references, taken as a whole at the time the application was filed, would have motivated or suggested to one of ordinary skill, at the time the present application was filed, combining these references, let alone having motivated the invention of the claims, let alone providing an expectation of success.

Green et al. (1999), the more recent of the primary references, fails to cite Platt et al. (1997). Neither Green et al. nor Platt et al. cite Rubin et al. (1997). Further, Platt et al. shows only methods of making a modified pectin. As is admitted in the Office Action admits on p. 9, neither Green et al. nor Rubin et al. shows a modified pectin. Therefore, one of ordinary skill in the art reading Platt et al. would have no motivation to combine Platt et al. with either of Green et al. or Rubin et al, let alone both.

Even had one of ordinary skill in the art, reading the cited references, been motivated at the time the present application was filed to combine these references, there was no suggestion that this combination would have been successful. The facts show that there is no suggestion from the prior art to combine the cited references to try the claimed method, and no suggestion of a reasonable expectation of success had the combination been made. As none of the cited references provides any motivation to one of ordinary skill in the art to have combined any elements of these primary references to arrive at Applicants' present claims, for at least this

reason also no *prima facie* case for obviousness of the claims has been established. Rather, making the combination is using Applicants' own specification as a blueprint to reconstruct the invention, which is impermissible hindsight.

For any of these reasons, claims 1, 23, 27, and 28 are not obvious in light of the combination of Green et al. or Rubin et al. in view of Platt et al. Claims 2-4, 7, 13, and 18-22, depend directly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter. Claims 24-26 depend directly from claim 23 and incorporate the subject matter of claim 23 and contain additional subject matter. Therefore, claims 2-4, 7, 13, 18-22, and 24-26 also are not obvious in light of the Green et al, or Rubin et al, and Platt et al.

Therefore rejection of claims 1-5, 7-9, 12, 13, and 15-28 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999) or Rubin et al. (U.S. patent number 5,639,737, 1994, issued 1997) in view of Platt et al. (PCT patent application number WO 97/34907, published 1997) and further in view of Ros et al. (Carbohyd. Res., 282:271-284, 1996)

The Office Action rejects claims 1-5, 7-10, 12, 13, and 15-28 under 35 U.S.C. §103(a) in light of Green et al. or Rubin et al. in view of Platt et al. and further in view of Ros et al. Applicants respectfully traverse.

Green et al., Rubin et al., and Platt et al. are characterized above. Ros et al. fails to cure any of the defects of Green et al., Rubin et al., or Platt et al. alone or in combinatrion, as is shown below.

Ros et al. shows the composition of the albedo of Spanish lemons (Ros et al. Abstract), how to remove pectin from lemons, how to prepare pectin fractions, and enzymatic hydrolysis of the pectin fractions (Ibid. p. 272-273). Ros et al. shows the composition of albedo from Spanish lemons (Ibid. p. 275-282).

Nowhere does Ros et al. teach or suggest any method for enhancing efficacy of a therapeutic treatment for cancer in a patient, the therapeutic treatment including chemotherapy, radiation therapy, surgery, and combinations of these. This reference never even mentions the words "cancer", "chemotherapy", "surgery", or "radiation therapy". Nowhere does this

reference teach or suggest a method of treating any human patient or any organism. This reference simply has nothing to do with cancer treatment at all.

In particular, Ros et al. fails to teach or suggest administering to the patient a therapeutically effective amount of a carbohydrate which binds to a galectin and administering the therapeutic treatment to the patient. This reference never even uses the word "galectin", let alone teach or suggest administering a carbohydrate which binds to a galectin.

As discussed above, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 916 F.2d 680, 16 U.S.PDQ 1430 (Fed. Cir. 1990). Applicants show below that none of these prior art references, taken as a whole at the time the application was filed, would have motivated or even suggested to one of ordinary skill combining these references, let alone have motivated the invention of the claims, let alone provided an expectation of success.

Green et al. (1999), the more recent of the primary references, fails to cite any of Platt et al. (1997), or Rubin et al. (1997). None of Green et al., Platt et al., or Rubin et al. cite Ros et al. (1996). Ros et al. shows only the composition of the albedo of Spanish lemons. There is nothing taught or suggested in Ros et al. about cancer or methods of treating cancer. Additionally, as is admitted in the Office Action on p. 10, none of Green et al., Rubin et al., or Platt et al. shows the use of enzymatically modified citrus pectins.

Therefore, the facts show that there is no teaching or suggestion from the prior art to combine the cited references to try the claimed method, let alone any teaching or suggestion of a reasonable expectation of success had the combination been made. As none of the cited references provides any motivation to one of ordinary skill in the art to have combined any elements of these primary references to arrive at Applicants' present claims, for at least this reason also no *prima facie* case for obviousness of the claims has been established. Rather, making the combination is using Applicants' own specification as a blueprint to reconstruct the invention, which is impermissible hindsight.

Further, in order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker,* 977

F.2d 1443; 1446 (Fed. Cir. 1992); 24 U.S.PQ2d 1443. Ros et al. shows only the composition of the albedo of Spanish lemons. Nowhere does Ros et al. show cancer, methods to treat cancer, therapeutic treatments, carbohydrates that bind to galectins, or administration to a patient of a carbohydrate that binds a galectin. To use Ros et al., a reference in a different field, as part of the present rejection is using the present application as a blueprint to reconstruct the claims, which is impermissible hindsight.

For any of these reasons, claims 1, 23, 27, and 28 are not obvious in light of the combination of Green et al. or Rubin et al. in view of Platt et al. and further in view of Ros et al. Claims 2-5, 7-10, 12, 13, and 15-22 depend directly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter. Claims 24-26 depend directly from claim 23 and incorporate the subject matter of claim 23 and contain additional subject matter. Therefore, claims 2-5, 7-10, 12, 13, 15-22, and 24-26 also are not obvious in light of the Green et al, or Rubin et al, and Platt et al. and Ros et al.

Therefore rejection of claims 1-5, 7-10, 12, 13, and 15-28 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Green et al. (Anti-Cancer Drug Design, 14:153-168, 1999) or Rubin et al. (U.S. patent number 5,639,737, 1994, issued 1997) in view of Platt et al. (PCT patent application number WO 97/34907, published 1997) and further in view of Renard et al. (Carbohyd. Res., 275:155-165, 1995)

The Office Action rejects claims 1-5, 7-9, 11-13, and 15-28 under 35 U.S.C. §103(a) in light of Green et al. or Rubin et al. in view of Platt et al. and further in view of Renard et al. Applicants respectfully traverse.

Green et al., Rubin et al., and Platt et al. are characterized above. Renard et al. fails to cure any of the defects of Green et al., Rubin et al., or Platt et al. alone or in any combination, as is shown below.

Renard et al. shows the composition of de-esterified apple, beet, and citrus pectins (Renard et al. p. 155 Abstract). Renard et al. shows commercial sources for these pectins, methods of purification, de-esterification, and acid hydrolysis, and chromotagraphic methods of detection (Ibid. p. 156-157).

Nowhere does Renard et al. teach or suggest any method for enhancing the efficacy of any therapeutic treatment for any cancer in a patient, and nowhere is any therapeutic treatment such as chemotherapy, radiation therapy, surgery, and combinations of these taught or suggested. This reference never even mentions the words "cancer", "chemotherapy", "surgery", or "radiation therapy". Nowhere does this reference show any method of treating any patient or in any organism. In fact, this reference has nothing to do with cancer treatment at all.

Renard et al. fails to teach or suggest any administering to any patient of any therapeutically effective amount of any carbohydrate which binds to a galectin and administering the therapeutic treatment to the patient. This reference never uses the word "galectin", let alone administering a carbohydrate which binds to a galectin.

As discussed above, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 916 F.2d 680, 16 U.S.PDQ 1430 (Fed. Cir. 1990). Applicants show below that none of these prior art references, taken as a whole at the time the application was filed, would have motivated or suggested combining these references, let alone have motivated the invention of the claims, let alone have provided an expectation of success.

Green et al. (1999), the most recent of the primary references, fails to cite any of Platt et al. (1997), or Rubin et al. (1997). None of Green et al., Platt et al., or Rubin. et al. cite Renard et al. (1995). Renard et al. shows only the composition of de-esterified apple, beet, and citrus pectins. There is nothing in Renard et al. that teaches or suggests any cancer or methods of treating cancer.

Therefore, the facts show that there is no suggestion from the prior art to combine the cited references to try the claimed method, and no suggestion of a reasonable expectation of success had the combination been made. As none of the cited references provides any motivation to one of ordinary skill in the art to have combined any elements of these primary references to arrive at Applicants' present claims, for at least this reason also no *prima facie* case for obviousness of the claims has been established. Rather, making the combination is using Applicants' own specification as a blueprint to reconstruct the invention, which is impermissible hindsight.

Further, in order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned. *In re Oetiker,* 977 F.2d 1443, 1446 (Fed. Cir. 1992); 24 U.S.PQ2d 1443. Renard et al. only shows the composition of de-esterified apple, beet, and citrus pectins. Nowhere does Renard et al. show cancer, methods to treat cancer, therapeutic treatments, carbohydrates that bind to galectins, or administration to a patient of a carbohydrate that binds a galectin. To use Renard et al., a reference in a different field, as part of the present rejection is using the present application as a blueprint to reconstruct the claims, which is impermissible hindsight.

For at least these reasons, claims 1, 23, 27, and 28 are not obvious in light of the combination of Green et al. or Rubin et al. in view of Platt et al. and further in view of Renard et al. Claims 2-5, 7-9, 11-13, and 15-22 depend directly or indirectly from claim 1 and incorporate the subject matter of claim 1 and contain additional subject matter. Claims 24-26 depend directly from claim 23 and incorporate the subject matter of claim 23 and contain additional subject matter. Therefore, claims 2-5, 7-9, 11-13, 15-22 , and 24-26 also are not obvious in light of the Green et al, or Rubin et al, and Platt et al. and Renard et al.

Therefore rejection of claims 1-5, 7-10, 12, 13, and 15-28 under 35 U.S.C. §103(a) can be withdrawn, an action which is respectfully requested.

Claims comply with 35 U.S.C. §112 ¶1

The Office Action on p. 2 rejects claims 4 and 23-28 under 35 U.S.C. §112 ¶1, alleging that there is no description of side chains dependent from the polymeric backbone.

Applicants respectfully traverse, and point out that possession of the invention is properly evaluated based on Applicants' own written description of the inventive matter, *viz.*, what was included in the specification as filed. *Manual of Patent Examining Procedure* §2163.01 (8th Ed. Rev.2, May 2, 2004).

Applicants' specification as originally filed on p. 5 lines 20-21 incorporates by reference U.S. patent application serial number 09/750,726 (Platt), now U.S. patent number 6,423,314. This reference shows oligomeric or polymeric species having dependent side chains of one or

more sugars such as galactose or arabinose. In particular, Platt shows a material having a cellulose backbone with dependent galactose terminated side chains.

Further, the specification as filed shows a group of materials with a substantially demethoxylated polygalacturonic acid backbone and dependent rhamnose residues and side chains having terminal glucose and arabinose units dependent from the backbone. See p. 6 lines 7-11 and formulas I, II, and III. One of ordinary skill in the art of biochemistry and molecular biology would have understood at the time the application was filed, that the repeating units having terminal glucose and arabinose units are side chains of the polygalacturonic acid backbone.

Even further, the specification shows pectin, a compound well known to one of ordinary skill in the art of biochemistry and molecular biology, and explains that pectin is a complex carbohydrate with a highly branched structure having a polygalacturonic backbone with numerous branching side chains dependent on the backbone. See p. 7 lines 7-9 in the specification as originally filed. Applicants' specification explains that pectin can be modified by various processes to have a more linearized substantially demethoxylated polygalacturonic backbone with dependent side chains of rhamnose residues. See p. 7 lines 10-14 in the specification as originally filed. Applicants' specification also incorporates by reference U.S. patent number 5,895,784 which shows modified pectin materials and techniques for their preparation. See p. 8 lines 4-22 in the specification as originally filed. The above facts show that Applicants' specification as filed provided ample support for the possession of the subject matter of these claims.

The Office Action on p. 3 alleges that there is no support in claim 24 for the term "homopolymer". Applicants respectfully traverse.

As a preliminary matter, a homopolymer is a polymer which contains only one type of monomer. Applicants assert that the specification as originally filed provides numerous examples of homopolymers. For example, the specification as originally filed on p. 6 and 7 provides formulas I and II that show polymers having only demethoxylated galacturonic acid. One of ordinary skill in the art of biochemistry or molecular biology at the time the present application was filed would have recognized both formulas I and II as homopolymers.

As such, the subject matter of the present claims is fully supported with respect to the requirements of 35 U.S.C. §112 ¶1, written description. Therefore rejection of claims 4 and 23-28 under 35 U.S.C. §112 ¶1 can properly be withdrawn, an action which is respectfully requested.

Claims comply with 35 U.S.C. §112 ¶2

The Office Action on p. 3 rejects claim 24 under 35 U.S.C. §112 ¶2. Applicants respectfully traverse.

As discussed above, a homopolymer is defined as a polymer which is formed from only one type of monomer. This term was well known to one of ordinary skill in the art of biochemistry and molecular biology at the time the present application was filed, because homopolymers played important roles in elucidation of the genetic code forty years ago and the distinction with heteropolymers and copolymers. Thus a first codon was elucidated by translating *in vitro* homopolymer poly(U) into homopolymer polyphenylalanine. These classical studies were well known many years prior to the filing of the present application, and are universally applied to natural and synthetic polymers.

Further, The Encyclopedia of Molecular Biology refers to homopolymers, for example, homopolymer tails used for joining DNA molecules *in vitro,* a copy of which is attached hereto as Appendix **A**. This reference shows homopolymers, oligo(dA) and oligo(dT). This reference was first published in 1994, before the present application was filed.

As one of ordinary skill in the art of biochemistry and molecular biology would understand the meaning of homopolymer, rejection of claim 24 under 35 U.S.C. §112 ¶2 can properly be withdrawn, an action which is respectfully requested.

Non-statutory double patenting issues

The Office Action on p. 12 rejects claims 1-5 and 7-28 under the judicially created doctrine of double patenting in view of U.S. patent number 6,680,306.

The Office Action on p.12 states that "... a timely filed Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome an actual or provisional rejection

based on a non-statutory double patenting ground ..." Accordingly, Applicants provide here a Terminal Disclaimer for co-owned issued patent having U.S. patent number 6,680,306.

Upon entry of the Terminal Disclaimer attached hereto, rejection under the judicially created doctrine of double patenting can properly be withdrawn, an action which is respectfully requested.

The Office Action on p. 13 rejects claims 1-5, 7-13, 15-19, 23, and 25-28 under the judicially created doctrine of double patenting in view of U.S. patent number 6,690,906 and Zetter (Annu. Rev. Med. 1998).

As a preliminary matter, U.S. patent number 6,690,906 (Tanaka et al.) pertains to the field of copiers and is not material to Applicants' application. Applicants respectfully request further information regarding this rejection.

Summary

On the basis of the foregoing reasons, Applicants respectfully submit that the pending claims are in condition for allowance, which is respectfully requested. If there are any questions regarding these remarks, the Examiners are invited and encouraged to contact Applicants' representative at the telephone number provided.

Respectfully submitted,

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Dated: August 15, 2006

Appendix A

homologous chromosomes The maternally and paternally derived chromosomes present in a diploid cell that bear equivalent genetic information, are similar in morphology, and pair during MEIOSIS.

homologous recombination Genetic RECOMBINATION that occurs between DNAs with long stretches of HOMOLOGY (e.g. between homologous chromosomes at MEIOSIS) and which is mediated by enzymes that show no particular sequence specificity (*cf.* site-specific recombination). It is also known as general recombination. Homologous recombination can be used to target introduced DNA to particular regions of the chromosome, thus disrupting selected genes. *See*: GENE KNOCKOUT.

homophilic binding (homotypic binding) Like-to-like binding. The concept has arisen from work on the NCAM CELL ADHESION MOLECULE, which binds to other NCAM molecules on other cells. This was originally shown by studies of liposomes containing the purified protein. Since then a number of proteins have been shown to exhibit this unusual type of interaction. In mechanistic terms it is likely that there are at least two sites involved in the binding, each of which could bind to its complementary site on the other molecule. Binding is therefore analogous to the lock-and-key mechanism (or heterophilic ligand–receptor binding) except that the two complementary sites are carried on the same molecule. The details are not well worked out in most systems, but in NCAM the IMMUNOGLOBULIN DOMAINS are clearly important.

homopolymer tailing A general method for joining DNA molecules *in vitro*. Complementary homopolymer sequences (e.g. oligo(dA), oligo(dT)) are added onto the respective 3′ termini of each DNA molecule to be joined. Such homopolymeric extensions are catalysed by TERMINAL DEOXYNUCLEOTIDYLTRANSFERASE.

Deng, G. & Wu, R. (1981) *Nucl. Acids Res.* 9, 4173–4188.

homotypic Like to like. Applied to binding of cell-surface adhesion molecules.

homozygote A DIPLOID cell or organism in which the two ALLELES at a given locus are identical. *Cf.* HETEROZYGOTE. *See*: MENDELIAN INHERITANCE.

homozygous *See*: HOMOZYGOTE.

Hoogsteen base pairing A nonstandard form of BASE PAIRING.

hordeivirus group From Latin *hordeum*, barley, after the type member barley stripe mosaic virus. MULTICOMPONENT VIRUSES with rigid rod-shaped particles 100–150 nm long and 20 nm in diameter. The infective genome comprises three species of (+)-strand linear RNA (Fig. H15). The product of RNA 1 (α) has homologies to RNA polymerases. The 5′ gene of RNA 2 (β) encodes the coat protein; the functions of the other three genes are unknown. RNA 3 (γ) varies in size according to virus strain (e.g. type strain, 3164 nucleotides; ND18 strain, 2791 nucleotides) and is bicistronic, the 5′ protein (87K or 74K depending on strain) having homologies to RNA replicases and the 3′ protein (unknown function) being translated from a subgenomic RNA 4 which is sometimes encapsidated. *See also*: PLANT VIRUSES.

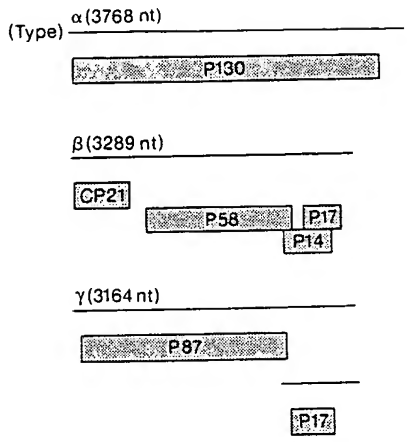

Fig. H15 Genome organization of barley stripe mosaic virus (BSMV). The lines represent the RNA species and the boxes the proteins (P) with M_r given as $\times 10^{-3}$; nt, nucleotides.

Atabekov, J.G. & Dolja, V.V. (1986) In *The Plant Viruses* (van Regenmortel, M.H.V. & Fraenkel-Conrat, H., Eds) Vol. 2, 397 (Plenum, New York).

Hordeum vulgare Barley.

horizontal transmission Transmission of viruses from one individual to another (*cf.* VERTICAL TRANSMISSION). Most horizontal transmissions occur by the respiratory route or the faecal–oral route, as viruses cannot penetrate the skin unaided and most easily enter the body through the naked cell surfaces available for gaseous exchange (lungs) or absorption of food (gut). Both respiratory viruses and some that cause systemic infections (measles: Paramyxoviridae; smallpox: Poxviridae) are spread by the respiratory route. Sexual transmission is important for a small number of viruses (HIV: Retroviridae; herpes simplex viruses types 1 and 2: Herpesviridae) when either free virus or infected cells are transmitted. Viruses are only transmitted through the skin when there is some 'mechanical' means of penetration. Mosquitoes transmit yellow fever virus (Flaviviridae) to primates; fleas and mosquitoes transmit myxoma virus (Poxviridae) to rabbits in the UK and Australia respectively. Virus-contaminated hypodermic needles, used medically or by intravenous drug abusers, or needles used for acupuncture or tattooing can also spread virus. *See also*: ANIMAL VIRUSES; ANIMAL VIRUS DISEASE.

hormone(s) Substances produced and released by one tissue which have an effect on another tissue. In humans they include the pituitary hormones (e.g. ADRENOCORTICORTICOTROPIN, FOLLICLE-STIMULATING HORMONE, GROWTH HORMONE, LUTEINIZING HORMONE, PROLACTIN, THYROID-STIMULATING HORMONE), and hormones produced by endocrine glands (e.g. THYROXINE, ADRENALINE, the STEROID HORMONES, INSULIN, and GLUCAGON).

THE ENCYCLOPEDIA OF Molecular Biology

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Appendix A

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Feldgasse 13, A-1238 Wien
Austria

First published 1994

Set by Semantic Graphics, Singapore
Printed in Great Britain at the Alden Press Limited
Oxford and Northampton
Bound by Hartnolls Ltd, Bodmin, Cornwall

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A catalogue record for this title
is available from both the British Library
and the Library of Congress

ISBN 0-632-02182-9